UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,229	01/23/2004	Daniel Dube	MC073YCA	9131

210 7590 01/05/2006

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
HOFFMAN, LEXINGTON A	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,229	DUBE ET AL.	
	Examiner	Art Unit	
	Lexington A. Hoffman	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,25,26 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,18-22,25 and 26* is/are rejected.

7)☒ Claim(s) *11-17 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application is a CON of PCT/CA03/01800, filed 11/19/03, and claims priority to 60/428, 611.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 22, 25, 26 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 02/094823. A compound of formula I is anticipated by the compounds of examples I, 2, 4, 6, 9 of table 1, p. 45 of '823.

Claims 1, 2, 22, 25, 26 are rejected under 35 U. S. C. 102(e) as being anticipated by '823 (ibid.). A compound of formula I is anticipated by the compound of examples 24 and 61 of table 2, p. 46 of '823.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6677351. Although the conflicting claims are not identical, they are not patentably distinct from each other because the core of formula I in each is identical and there is significant overlap in the Markush language. The 2 definitions of Ar in '351, are found in the instant, R is identical, and all the limitations of R1 in the prior are found in the instant. R2 of '351 is analogous to "Y" of the instant; -COOR4 of instant Y is encompassed by the Markush option -C(O)-O-C1-6alkyl of '351. R3 of '351 is analogous to R2 of the instant, and the only of option of R3 in the prior not found in the instant is -OH. '351 shows two R groups on the phenyl ring attached to the napthyridine core whereas the instant shows only one. Both the instant and prior share the options of H, halogen, and C1-C6 alkyl as potential substitutions on the ring and can thus result in identical compounds. No indication is given as to why any particular substitution pattern brings about unexpected result over another. The prior art has two R groups (R4 and R5) inserting on the napthyridine core, whereas the instant specifies none. Both R4 and R5 can be H, thus making it identical to the instant, and no indication has been given as to why

substitutions on this ring confer unexpected results versus having only hydrogen attached to the ring. Since '351 is drawn to inhibitors of phosphodiesterase IV (like the instant), it would be obvious to modify the prior claim to arrive at the instant with a reasonable expectation of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. *nature of the invention*

The instant invention is drawn to PDE-IV inhibiting napthyridine compound and the use of compositions thereof to treat/prevent various diseases/disorders.

b. *state of the prior art and level of skill in the art*

PDE-IV inhibitors have been reviewed Houslay, et al., (2005), and their use in specific diseases have been described in numerous publications. While PDE-IV inhibitors have been identified as a potential therapeutic target in a number of diseases, there is no known compound effective in treating all the disorders listed in claim 25.

Regarding claim 26, Houslay, et al., state that Rolipram improves working and reference memory (p. 1515).

The level of skill in the PDE-IV inhibiting art is high.

c. *predictability/unpredictability of the art*

Unpredictability is well recognized in the enzyme inhibitor art. A slight change in structure can lead to drastic change in effect. The PDE-IV IC50 of applicant's own structurally similar compounds ranged from 0.01nM to 2300nM (specification, p.28).

d. *guidance/working examples*

The preparation of the compounds is described in the specification. Inhibition of human PDEIV was described on p. 28. The effects of the instant compounds on pulmonary inflammation in guinea pigs was described on p. 27, and TNF-α inhibition was described on pp. 35-26. Other than the pulmonary inflammation, the effect of the compounds on a disease state (rather than their influence on a biological pathway in a non-clinical application) was not disclosed. No data was provided as to how the inventive compounds enhance cognition.

e. *breadth of the claims*

Applicant's assertion that the inventive compounds are useful in treating the myriad diseases with diverse etiologies recited in the claims is not commensurate with the objective enablement, particularly in view of the unpredictability of the art, limited working examples, and that no known drug can treat all the recited disorders. While Houslay, et al., discuss several potential uses for PDE-IV inhibitors, they also state that different disease processes involve different PDE-IV subtypes. They further write,

"Hardly any information is known, from studies on actual patients, regarding PDE4 subtype expression patterns on cells and tissues. This is clearly an important deficit that needs correcting." (p. 1515). While a PDE-IV inhibitor has been shown to improve working and reference memory, the claims embrace "cognition", a much broader term.

Among the claimed disorders are cancer, cachexia, and muscle wasting. No data was provided to indicate how the compounds would treat such disorders. Meijsing, et al., (2002), investigated the use of a PDE-IV inhibitor in treating tumor growth and cachexia. They found the drug "did not revert any of the decreases in tissue weights associated with tumour [sic] burden", concluded PDE-IV inhibitors are not efficacious in preventing or stopping cancer-mediated cachexia (p. 57).

Hypersecretion of gastric acid is also claimed. Again, no data/mechanism is described to indicate how the compounds would treat this disorder. Ochi, et al., (2005), found that cAMP is necessary for induction of gastric acid secretion (abstract). Since PDE-IV inhibitors terminate cAMP activity (specification, p. 1), this would imply (in the absence of any information to the contrary), that inhibition of PDE-IV could possibly exacerbate gastric acid hypersecretion rather than ameliorate it.

Arterial restenosis and atherosclerosis are claimed. While PDE-V inhibitors have been suggested to improve vascular function (Vlachopoulos, et al., 2004, abstract), and PDE-III inhibitors may play a role as well (Kayanoki, et al., 1997, abstract), applicant has provided no information to indicate why PDE-IV inhibition is effective.

These are just few examples from the myriad diseases claimed.

Claim 25 is also drawn to prevention of the diseases. To prevent a disorder, one would have to identify the subjects likely to acquire the disorder, administer the compound, and then demonstrate the subject did not acquire the disorder as a direct result of receiving the inventive compound. No such data is provided. As written, the claim would read on the entire population, and since it not necessarily safe to give a drug to all members of the population (pediatric/geriatric patients may have contraindications, and they or other patients may have concurrent disease states and/or treatment regimes that would preclude safe administration of the instant compounds), one would not be able to use the invention as claimed.

f. *quantity of undue experimentation*

Since insufficient teaching and guidance have been provided, one of skill in the art would not able to use the compounds without undue experimentation.

Claim Objections

Claims 11-17, 29 are objected to as being dependent on a rejected base claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lexington A. Hoffman whose telephone number is 571-272-4328. The examiner can normally be reached on Monday-Friday 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecelia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

***

Lexington Hoffman
Art Unit 1625

LH

12/27/05

Cecilia Tsang
Supervisory Patent Examiner
Art Unit 1625